

## AMENDMENT

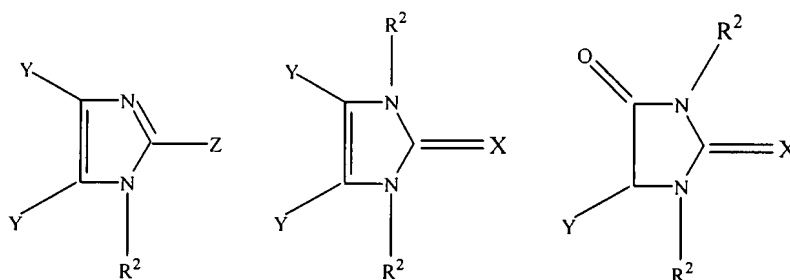
### Amendments to the Claims

*In the claims, please make the following amendments:*

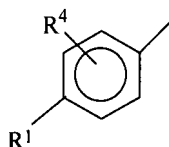
### Claims.

Claims 1-53 (canceled)

54. (currently amended) A method for inhibiting cell adhesion in a mammal which comprises administering to the mammal a pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of one or more methimazole derivatives[[,]] ~~and/or~~ cyclic thione derivatives, ~~or~~ and mixtures thereof, in an amount effective for ~~prevention~~, inhibition or suppression of cell adhesion, wherein the method is used to treat a cardiovascular disease in a mammal in need of such treatment, wherein the methimazole derivatives have the structural formulae:



wherein Y is selected from H, C1 -C4 alkyl C1 -C4 substituted alkyl, --NO<sub>2</sub>, and the phenyl moiety:



wherein no more than one Y group in said active compound may be the phenyl moiety;

R<sup>1</sup> is selected from H, -OH, halogens (F, Cl, Br or I), C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl,

C<sub>1</sub>-C<sub>4</sub> ester or C<sub>1</sub>-C<sub>4</sub> substituted ester; R<sup>2</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub>

substituted alkyl; R<sup>3</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl or -CH<sub>2</sub>Ph

(wherein Ph is phenyl); R<sup>4</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> substituted alkyl; X is

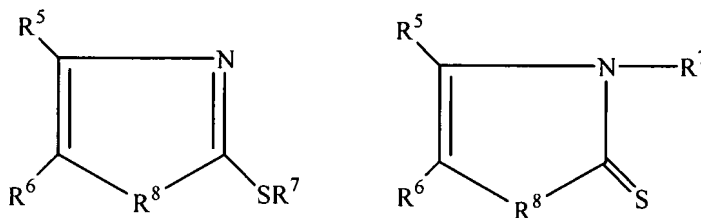
selected from S or O; Z is selected from -SR<sup>3</sup>, -OR<sup>3</sup>, S(O)R<sup>3</sup> or C<sub>1</sub>-C<sub>4</sub> alkyl; and wherein

at least two of the R<sup>2</sup> and R<sup>3</sup> groups on said compound are C<sub>1</sub>-C<sub>4</sub> alkyl when Y is not a

phenyl moiety, and at least one Y is -NO<sub>2</sub> when Z is alkyl; together with a

pharmaceutically-acceptable carrier; and

wherein the cyclic thione derivatives have the structural formulae:

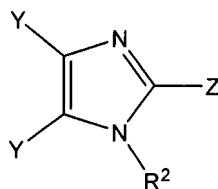


wherein R<sup>5</sup> is selected from CH<sub>3</sub>, CH<sub>3</sub>; Ph, H; H, and a phenyl moiety; wherein R<sup>6</sup> is

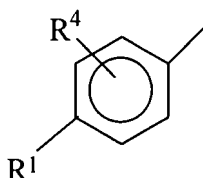
selected from CH<sub>3</sub>, CH<sub>3</sub>; Ph, H; H, and a phenyl moiety; wherein R<sup>7</sup> is selected from H

and CH<sub>3</sub>; and R<sup>8</sup> is selected from O, S, NH, and NCH<sub>3</sub>.

55. (previously presented) The method of claim 54 wherein the compound has a formula:



wherein Y is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl, -NO<sub>2</sub>, and the phenyl moiety:



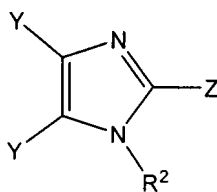
and wherein no more than one Y group in said active compound may be the phenyl moiety; R<sup>1</sup> is selected from the group consisting of H, -OH, halogens, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> substituted alkyl; R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl, and a phenyl moiety; R<sup>4</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> substituted alkyl; and Z is selected from -SR<sup>3</sup> and -OR<sup>3</sup>; R<sup>3</sup> is H; and wherein R<sup>2</sup> in said compound is C<sub>1</sub>-C<sub>4</sub> alkyl when Y is not a phenyl moiety; and a pharmaceutically-acceptable carrier

~~methimazole derivatives and/or cyclic thione derivatives are selected from the group consisting of tautomeric methimazole derivatives, non-tautomeric methimazole derivatives, and non-tautomeric cyclic thione derivatives, and combinations thereof.~~

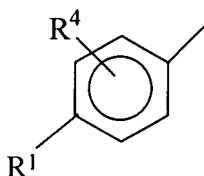
56. (withdrawn) A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to the mammal a pharmaceutical composition comprising methimazole derivatives and/or cyclic thione derivatives are selected from the group consisting of tautomeric methimazole derivatives, non-tautomeric methimazole derivatives, and non-tautomeric cyclic thione derivatives, and combinations thereof.
57. (currently amended) The method according to claim 55, wherein the cardiovascular disease is atherosclerosis, ~~the disease or condition is one or more of acute lung injury, allergic rhinitis, Alzheimer's disease, arthritis, asthma, atherosclerosis, autoimmune glomerulonephritis, Behcet's disease, cancer, cerebral infarcts, chronic hepatitis, cirrhosis, cutaneous anaphylaxis reaction, cutaneous vasculitides, delayed type hypersensitivity reaction, diabetes, disseminated intravascular coagulation, eosinophilic granuloma of the lung, gastritis, giant cell arteritis, Graves' disease, haemorrhagic shock, hypertensive vascular disease, hypothyroidism, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory dermatoses, intestinal infarcts, Kawasaki's disease (mucocutaneous lymph node syndrome), lymphoid interstitial pneumonia, malaria, meningitis, multiple sclerosis, myocardial infarcts, organ transplantation (host vs. graft and graft vs. host), polyarteritis nodosa, polymyositis/dermatomyositis, psoriasis, pulmonary infarcts, renal infarcts, reperfusion injury following ischemia, Rickettsial vasculitis, sarcoidosis, sepsis, sjogren's disease, stroke, systemic lupus erythematosus, thermal injury (burns), thromboangiitis obliterans (Buerger's disease), thrombosis, thyroiditis, tuberculosis, vasculitis, and Wegner's granulomatosis.~~

58. (currently amended) ~~A method of preventing, inhibiting or suppressing cell adhesion in a mammal comprising the step of administering to the mammal a pharmaceutical composition comprising methimazole derivatives and/or cyclic thione derivatives which are selected from the group consisting of tautomeric methimazole derivatives, non-tautomeric methimazole derivatives, and non-tautomeric cyclic thione derivatives, and combinations thereof, in an amount effective for prevention, inhibition or suppression of cell adhesion,~~ The method according to claim 54, wherein the cell adhesion is VCAM-1 mediated and a pharmaceutically acceptable carrier.
59. (previously presented) The method according to claim 58, wherein the cell adhesion is mediated by VCAM-1 and E-selectin.
60. (previously presented) The method according to claim 59, wherein the cell adhesion is IRF-1 dependent VCAM-1 mediated cell adhesion.
61. (currently amended) The method according to claim 54, wherein the cell adhesion is A ~~method of preventing, inhibiting or suppressing cytokine-induced cell adhesion in a mammal comprising the step of administering to the mammal a pharmaceutical composition comprising methimazole derivatives and/or cyclic thione derivatives which are selected from the group consisting of tautomeric methimazole derivatives, non-tautomeric methimazole derivatives, and non-tautomeric cyclic thione derivatives, and combinations thereof, in an amount effective for prevention, inhibition or suppression of cell adhesion, wherein the cell adhesion is VCAM-1 mediated and a pharmaceutically acceptable carrier.~~

62. (currently amended) The method according to claim 61, wherein the cell adhesion is mediated by VCAM-1 and E-selectin.
63. (currently amended) The method according to claim 62, wherein the cell adhesion is IRF-1 dependent VCAM-1 mediated cell adhesion.
64. (currently amended) The method according to claim 61, wherein the cytokine is TNF-alpha.
65. (canceled).
66. (canceled)
67. (canceled)
68. (canceled)
69. (withdrawn) The method according to claims 55, 58 or 61, wherein the pharmaceutical composition comprises a safe and effective amount of the tautomeric methimazole derivative:

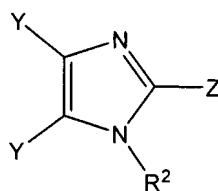


wherein Y is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl, -NO<sub>2</sub>, and the phenyl moiety:

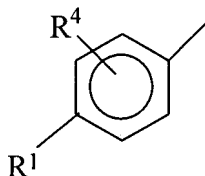


and wherein no more than one Y group in said active compound may be the phenyl moiety;  $R^1$  is selected from the group consisting of H, -OH, halogens,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl;  $R^2$  is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  substituted alkyl, and a phenyl moiety;  $R^3$  is H;  $R^4$  is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl; and Z is selected from  $-SR^3$  and  $-OR^3$ ; and wherein  $R^2$  in said compound is  $C_1$ - $C_4$  alkyl when Y is not a phenyl moiety; and a pharmaceutically-acceptable carrier.

70. (withdrawn) The method according to claims 55, 58 or 61, wherein the pharmaceutical composition comprises a safe and effective amount of the non-tautomeric methimazole derivative



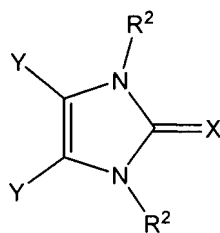
wherein Y is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  substituted alkyl,  $-NO_2$ , and the phenyl moiety:



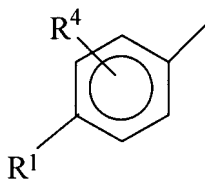
and wherein no more than one Y group in said active compound may be the phenyl moiety;  $R^1$  is selected from the group consisting of H, -OH, halogens,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl;  $R^2$  is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$

substituted alkyl, and a phenyl moiety;  $R^3$  is selected from the group consisting of  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  substituted alkyl, and  $-CH_2Ph$ ;  $R^4$  is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl; and Z is selected from  $-SR^3$ ,  $S(O)R^3$ ,  $-OR^3$  and  $C_1$ - $C_4$  alkyl; and wherein at least two of the  $R^2$  and  $R^3$  groups in said compound are  $C_1$ - $C_4$  alkyl when Y is not a phenyl moiety, and at least one Y is  $-NO_2$  when Z is alkyl; and a pharmaceutically-acceptable carrier.

71. (withdrawn) The method according to claims 55, 58, or 61, wherein the pharmaceutical composition comprises a safe and effective amount of the non-tautomeric cyclic thione derivative



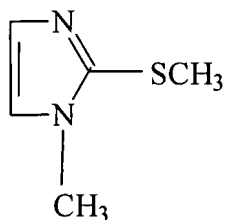
wherein Y is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  substituted alkyl,  $-NO_2$ , and the phenyl moiety:



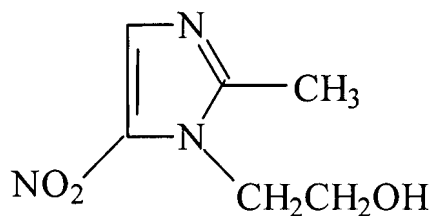
and wherein no more than one Y group in said active compound may be the phenyl moiety;  $R^1$  is selected from the group consisting of H,  $-OH$ , halogens,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl;  $R^2$  is selected from the group consisting of  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  substituted alkyl, and a phenyl moiety;  $R^4$  is selected from the group consisting of H,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  substituted alkyl; X is S; and a pharmaceutically-acceptable carrier.



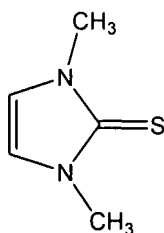
72. (withdrawn) The method according to claims 69 or 70, wherein Z is  $SR^3$  and Y is H.
73. (withdrawn) The method according to claim 72, wherein  $R^3$  is  $C_1$ - $C_4$  alkyl.
74. (withdrawn) The method according to claim 73, wherein  $R^3$  is methyl.
75. (withdrawn) The method according to claim 74, wherein the  $R^2$  group is methyl.
76. (withdrawn) The method according to claim 74, wherein both  $R^2$  groups are methyl.
77. (withdrawn) The method according to claim 70, wherein the active compound has the formula



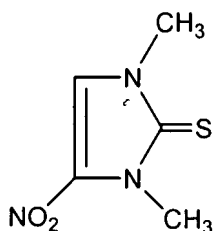
78. (withdrawn) The method according to claim 70, wherein the active compound has the formula



79. (withdrawn) The method according to claim 71, wherein the active compound has the formula:

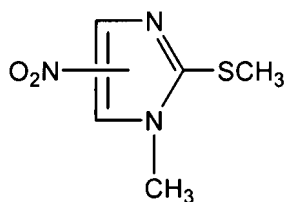


80. (withdrawn) The method according to claim 71, wherein the active compound has the



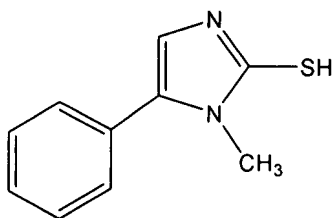
formula:

81. (withdrawn) The method according to claim 70, wherein the active compound has the  
formula:

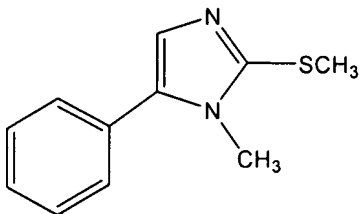


82. (withdrawn) The method according to claims 69 or 70, wherein Z is SR<sup>3</sup> and one of the Y groups is the phenyl moiety.
83. (withdrawn) The method according to claim 71, wherein R<sup>1</sup> and R<sup>4</sup> are H.

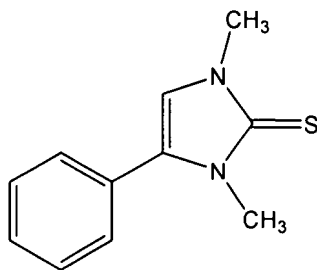
84. (withdrawn) The method according to claim 70, wherein Z is  $\text{SR}^3$  and  $\text{R}^3$  is a methyl, and one of the Y groups is the phenyl moiety wherein  $\text{R}^1$  and  $\text{R}^4$  are H, and the  $\text{R}^2$  group is methyl.
85. (withdrawn) The method according to claim 69 or 70, wherein Z is  $\text{SR}^3$  and  $\text{R}^3$  is H, and one of the Y groups is the phenyl moiety wherein  $\text{R}^1$  and  $\text{R}^4$  are H, and the  $\text{R}^2$  group is methyl.
86. (withdrawn) The method according to claim 71, wherein one of the Y groups is the phenyl moiety, wherein  $\text{R}^1$  and  $\text{R}^4$  are H, and both  $\text{R}^2$  groups are methyl.
87. (withdrawn) The method according to claim 69, wherein the active compound is:



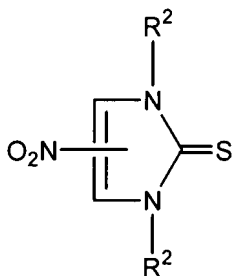
88. (withdrawn) The method according to claim 70, wherein the active compound is



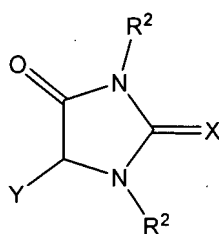
89. (withdrawn) The method according to claim 71, wherein the active compound is



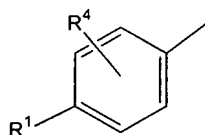
90. (withdrawn) The method according to claims 69, 70, or 71, wherein the pharmaceutical composition is in prodrug form.
91. (withdrawn) The method according to claims 69, 70, or 71, wherein the pharmaceutical composition comprises from about 0.01% to about 25% of the active compound and from about 75% to about 99.99% of the pharmaceutically-acceptable carrier.
92. (withdrawn) The method according to claim 71, wherein the pharmaceutical composition comprises a safe and effective amount of an active compound having the formula:



93. (withdrawn) The method according to claims 55, 58, or 61, wherein the pharmaceutical composition comprises a safe and effective amount of

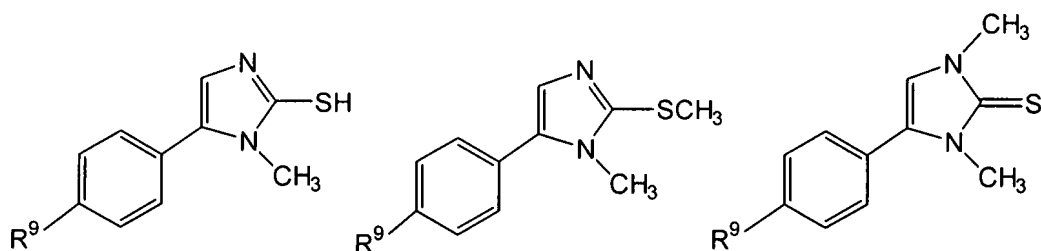


wherein Y is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl, -NO<sub>2</sub>, and the phenyl moiety:



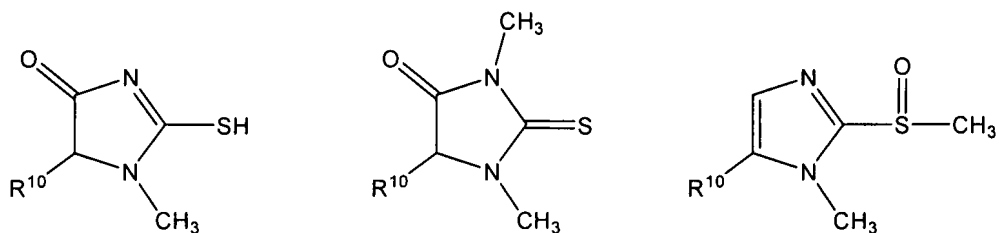
R<sup>1</sup> is selected from the group consisting H, -OH, halogens, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> substituted alkyl, C<sub>1</sub>-C<sub>4</sub> ester and C<sub>1</sub>-C<sub>4</sub> substituted ester; R<sup>2</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl and C<sub>1</sub>-C<sub>4</sub> substituted alkyl; R<sup>4</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl and C<sub>1</sub>-C<sub>4</sub> substituted alkyl; X is S; and wherein the R<sup>2</sup> groups in said compound are C<sub>1</sub>-C<sub>4</sub> alkyl when Y is not a phenyl moiety; and a pharmaceutically acceptable carrier.

94. (withdrawn) The method according to claims 55, 58 or 61, wherein the active compound is selected from the group consisting of



wherein  $R^9$  is selected from the group consisting of -OH, -M and -OOCCH<sub>2</sub>M; wherein M is selected from F, Cl, Br and I.

95. (withdrawn) The method according to claims 55, 58, or 61, wherein the active compound is selected from the group consisting of



wherein  $R^{10}$  is selected from the group consisting of H, -NO<sub>2</sub>, Ph, 4-HOPh and 4-MPh, wherein M is selected from F, Cl, Br and I.

96. (withdrawn) A method of treating a condition involving vascular adhesion of leukocytes, comprising: (a) identifying a subject suspected of having a condition involving aberrant leukocyte adhesion to vascular endothelium; and (b) administering to the subject an amount of a pharmaceutical composition comprising a methimazole derivatives and/or cyclic thione derivatives are selected from the group consisting of tautomeric methimazole derivatives, non-tautomeric methimazole derivatives, and non-tautomeric cyclic thione derivatives, and combinations thereof, sufficient to decrease cell surface expression of at least one of VCAM-I and E-selectin on endothelial cells, thereby reducing adhesion of leukocyte cells to vascular endothelium.
97. (withdrawn) The method according to claim 94, wherein one or more additional active ingredients are combined with the composition of the present invention, either

administered separately or in the same pharmaceutical composition, selected from the group comprising (a) VCAM-1 antagonists; (b) steroids; (c) immunosuppressants; (d) antihistamines; (e) non-steroidal anti-asthmatics; (f) non-steroidal antiinflammatory agents (NSAIDs); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors; (j) cholesterol lowering agents; (k) anti-diabetic agents; (l) preparations of interferon beta; (m) anticholinergic agents; and (n) antibiotics.

98. (withdrawn) A method of screening for compounds capable of ~~preventing~~, inhibiting or suppressing VCAM-1 mediated cell adhesion or preventing, inhibiting or suppressing cell adhesion-associated inflammation in a mammal, comprising:

- (a) contacting the mammal with a test compound;
- (b) measuring an effect of the test compound on leukocyte adhesion or migration or both; and
- (c) determining whether the test compound is an inhibitor of the adhesion or migration activities or both of the leukocytes.

99. (withdrawn) The method according to claim 43, wherein the measuring an effect of the test compound comprises one or more of measuring IRF-1 RNA expression levels; measuring IRF-1 protein expression levels; measuring IRF-1 dependent VCAM-1 promoter activation; measuring cytokine -increased IRF-1 RNA expression levels; measuring cytokine -increased IRF-1 protein expression levels; measuring cytokine-increased IRF-1 dependent VCAM-1 promoter activation; measuring TNF-alpha-increased IRF-1 RNA expression levels; measuring TNF-alpha-increased IRF-1 protein

expression levels; and measuring TNF-alpha-increased IRF-1 dependent VCAM-1 promoter activation.

100. (withdrawn) The method according to claim 96, wherein the measuring an effect of the test compound comprises one or more of measuring VCAM-1 RNA expression levels; measuring cytokine-increased VCAM-1 protein expression levels; measuring cytokine-increased VCAM-1 promoter activation measuring TNF-alpha-increased VCAM-1 RNA expression levels; measuring TNF-alpha increased VCAM-1 protein expression levels; and measuring TNF-alpha increased VCAM-1
101. (withdrawn) A method of screening for compounds capable of cell adhesion inhibitory activity in VCAM-1 expressing cells, comprising:
  - (a) contacting VCAM-1-expressing cells with a test compound;
  - (b) contacting the VCAM-1-expressing cells to VCAM-1 ligand expressing cells;
  - (c) measuring an effect of the test compound on binding of the VCAM-1-expressing cells to VCAM-1 ligand expressing cells; and
  - (d) determining whether the test compound is an inhibitor of the binding activities of the VCAM-1-expressing cells to VCAM-1 ligand expressing cells.
102. (withdrawn) The method according to claim 99, comprising the further step prior to, concurrently with or subsequently to addition of the test compound, of contacting VCAM-1-expressing cells with a cytokine capable of inducing expression of VCAM-1.
103. (withdrawn) The method according to claim 100, wherein the cytokine is TNF-alpha.



104. (withdrawn) The method according to claim 101, wherein the VCAM-1-expressing cells are selected from the group comprising nonimmune target tissue cells, endothelial cells, and epithelial cells.
105. (withdrawn) The method according to claim 101, wherein the VCAM-1-expressing cells are human aorta endothelial cells (HAEC).
106. (withdrawn) The method according to claim 101, wherein the VCAM-1 ligand expressing cells are leukocytes.
107. (withdrawn) The method according to claim 101, wherein the cells are allowed to remain in contact for at least 30 minutes.